

A Versatile Linkage Strategy for Solid-Phase Synthesis of *N,N*-Dimethyltryptamines and β -Carbolines

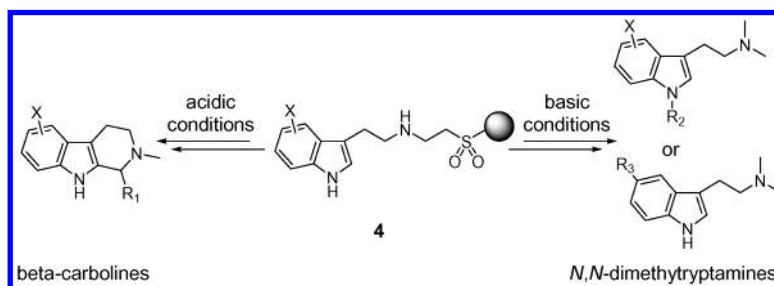
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ABSTRACT



Various tryptamines are captured by a vinylsulfonylmethyl polystyrene resin, generating a safety-catch linkage. β -Carbolines can be formed from **4** by a Pictet–Spengler reaction with the introduction of R_1 . Tryptamine **4** can also be derivatized by acylation or copper-mediated coupling to introduce R_2 . If $X = \text{Br}$, Suzuki coupling can be used to introduce R_3 . After derivatization, the indole derivatives are activated with methyl iodide and released under mild basic condition.

The tryptamine and β -carboline scaffolds are present in many naturally and synthetically derived molecules with interesting biological activities.¹ Consequently, many solid-phase synthetic approaches have been developed to generate small molecules containing these core structures.^{2–4} However, these approaches still have limitations with regards to functionalization of the indole scaffolds. For example, current solid-

phase methodologies for synthesizing β -carbolines derivatives use linkers that leave a polar functional group (e.g., COOH , CONH_2) after cleavage; the solid-phase synthesis of tryptamine analogues involves attaching the molecule onto resin either through a linkage at the indole nitrogen or an ester/amide linkage on the benzo ring. Herein we report a novel and versatile safety-catch linkage strategy that can be used to generate libraries of functionalized *N,N*-dimethyltryptamines and β -carbolines in a simple and straightforward manner.

Our approach starts with the synthesis of different tryptamine scaffolds (Scheme 1) in three facile steps using previously reported protocols.⁵ Commercially available indoles **1** were reacted with oxalyl chloride in refluxing ether. The resulting indole oxalyl chlorides were filtered and treated

(1) (a) *The Alkaloids, Chemistry and Physiology*; Manske, R. H. F., Ed; Academic Press: New York, 1981; Vol. XX. (b) Oh, S. J.; Ha, H.-J.; Chi, D. Y.; Lee, H. K. *Curr. Med. Chem.* **2001**, *8*, 999–1034. (c) Faust, R.; Garratt, P. J.; Jones, R.; Yeh, L.-K. *J. Med. Chem.* **2000**, *43*, 1050–1061.

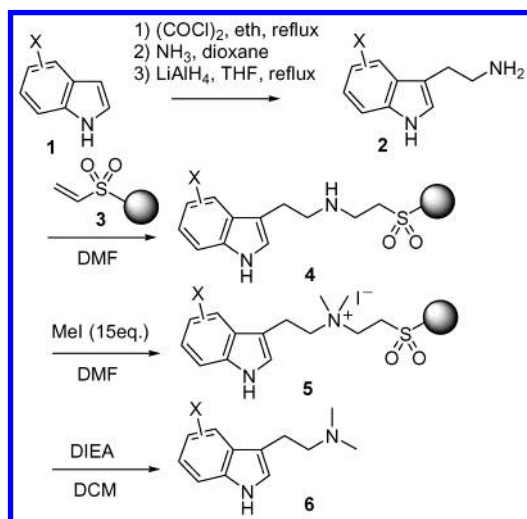
(2) (a) Mohan, R.; Chou, Y.-L.; Morrissey, M. M. *Tetrahedron Lett.* **1996**, *37*, 3963–3966. (b) Yang, L.; Guo, L. *Tetrahedron Lett.* **1996**, *37*, 5041–5044.

(3) (a) Zhang, H.-C.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4449–4452. (b) Smith, A. L.; Stevenson, G. I.; Lewis, S.; Patel, S.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2693–2696.

(4) The following work was published after the submission of this manuscript and describes a similar linkage strategy: Connors, R. V.; Zhang, A. J.; Shuttleworth, S. J. *Tetrahedron Lett.* **2002**, *43*, 6661–6663.

(5) Slassi, A.; Edwards, L.; O'Brien, A.; Meng, C. Q.; Xin, T.; Seto, C.; Lee, D. K. H.; MacLean, N.; Hynd, D.; Chen, C.; Wang, H.; Kamboj, R.; Rakshit, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1707–1709.

Scheme 1



with ammonia in dioxane to give the corresponding indole oxalyl amides. These were again filtered and reduced to the corresponding tryptamines **2** using lithium aluminum hydride in refluxing THF. After aqueous workup, the crude tryptamines were directly mixed with vinylsulfonylmethyl polystyrene resin **3** (Novabiochem).⁶ This also served as a purification step, as only the fully reduced tryptamines were captured onto the resin, affording **4**. Activation of the safety catch linker can be achieved by treatment with excess methyl iodide to form the quaternary ammonium salt **5**, though other alkylating agents have been used in the past.⁶ A Hoffman elimination using *N,N*-diisopropylethylamine releases tryptamine **6** from the resin. The yield of the cleaved products ranged from 10% to 20% overall, based on the resin-loading level of **4**. A variety of commercially available indoles with either electron-donating or electron-withdrawing functional groups on the benzo ring as well as alkyl and aryl groups at the C-2 position are compatible with this scheme (Figure 1). Purity of the resin-bound indoles is determined by cleaving a small amount of resin and subjecting the product to LCMS.

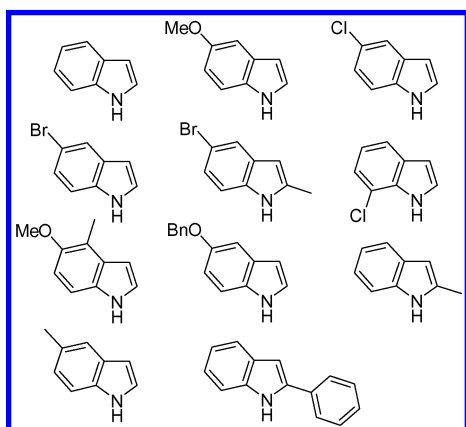
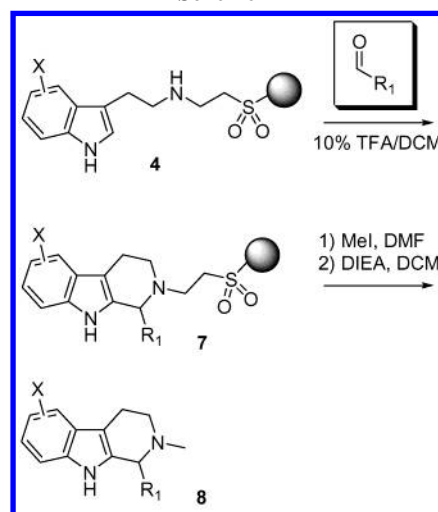


Figure 1. Indoles used as precursors for the tryptamine scaffolds.

All scaffolds in Figure 1 were tested to give >90% purity as analogues of tryptamine **6**.

The safety-catch linkage described here is stable to acidic conditions. Treatment of **4** with aldehydes in 1–10% trifluoroacetic acid (TFA) in dichloromethane (DCM) at room temperature for 12 h affords the β -carboline scaffold **7** through a Pictet–Spengler reaction⁷ without premature cleavage of the molecule from the solid support (Scheme 2). Activation of the resin followed by Hoffman elimination

Scheme 2



yielded β -carboline **8**. Indoles with electron-rich substituents (e.g., alkoxy groups) tend to react with 1% TFA/DCM; other indoles with relatively electron-neutral substituents (e.g., alkyl, aryl) or electron-poor substituents (e.g., halides) require 5–10% TFA/DCM. Several alkyl and aryl aldehydes were validated to give products with purity over 80% and 10–20% purified yield when tested with unsubstituted tryptamine derivatized resin **4** (Figure 2).

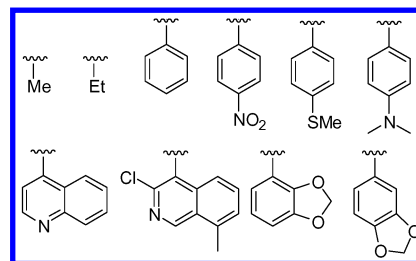
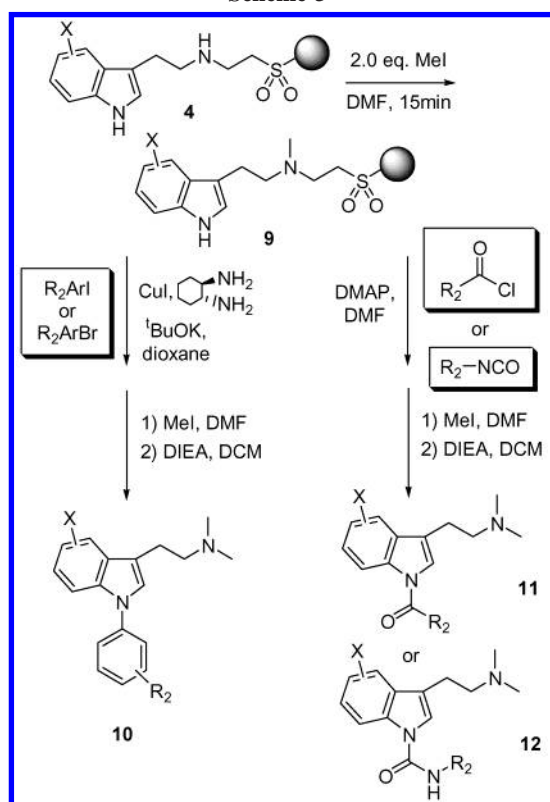


Figure 2. R_1 introduced through aldehydes.

Resin-bound tryptamine **4** can be monomethylated by treatment with 2.0 equiv of methyl iodide in DMF for 15 min at room temperature. The resulting product (**9**) was derivatized at the indole nitrogen by two different methods (Scheme 3). A copper-mediated coupling with aryl bromides

Scheme 3



or aryl iodides (depending on commercial availability) introduced an R_2 aryl substituent.⁸ The reaction involved heating the resin and the aryl bromide/iodide in the presence of copper(I) iodide, *trans*-1,2-diaminocyclohexane, and potassium *tert*-butoxide in anhydrous dioxane at 80 °C for 1 day. Alternatively, the indole nitrogen can be acylated with acid chlorides and isocyanates using 10 equiv of *N,N*-(dimethylamino)pyridine as the base in DMF at 80 °C for 12 h. Both the *N*-aryl bond and the *N*-acyl bond are stable in subsequent activation and cleavage steps. Both reactions are compatible with a variety of building blocks, generating products with over 80% purity and 10–20% purified yield when tested with unsubstituted tryptamine resin 9 (Figure 3).

When X is a bromine, resin-bound monomethylated tryptamine 9 can undergo derivatization through Suzuki coupling using tris(dibenzylideneacetone) dipalladium(0) as the catalyst and 2-(dicyclohexylphosphino)biphenyl as the ligand (Scheme 4).⁹ The resin, boronic acid, catalyst, and ligand were reacted in anhydrous dioxane in the presence of dry K_3PO_4 at 80 °C for 1 day. Eight boronic acids were tested for this reaction, and all of them afforded the expected products with purity over 80% and yielded between 10%

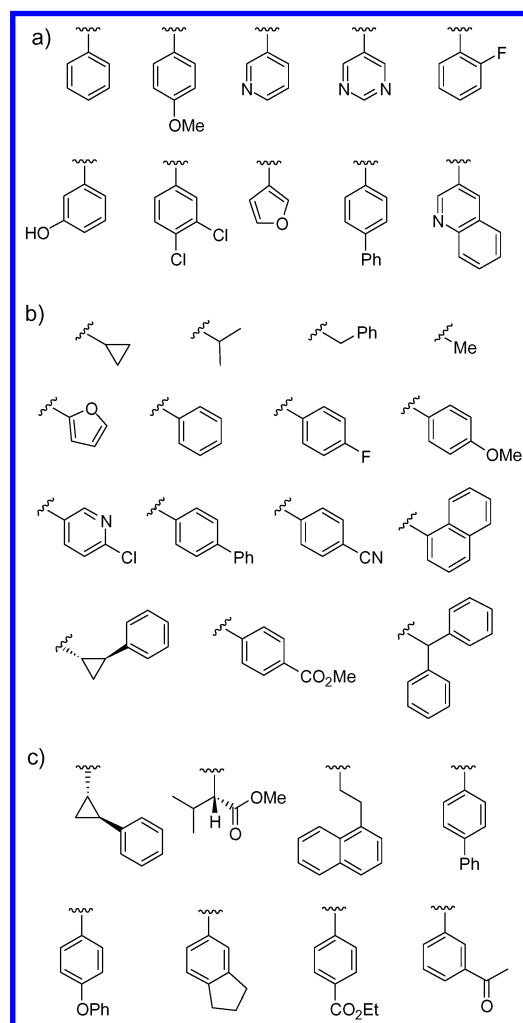
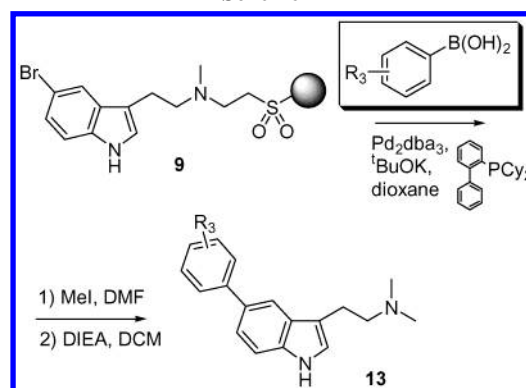


Figure 3. (a) R_2 Ar introduced through aryl bromides and aryl iodides. (b) Representative R_2 introduced through acid chlorides. (c) Representative R_2 introduced through isocyanates.

Scheme 4



and 20% after purification when tested with 5-bromo-tryptamine derivatized resin 9.

In conclusion, we have described a novel linkage strategy for making *N,N*-dimethyltryptamines and β -carbolines. The

(6) Kroll, F. E. K.; Morphy, R.; Rees, D.; Gani, D. *Tetrahedron Lett.* **1997**, 38, 8573–8576.

(7) Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, 44, 2030–2036.

(8) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, 123, 7727–7729.

(9) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, 65, 1158–1174.

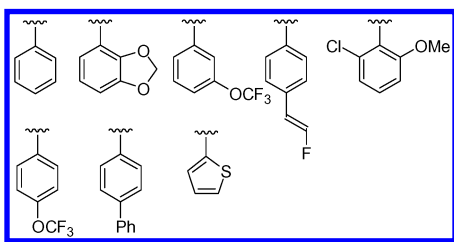


Figure 4. R_3 introduced through boronic acids.

linkage utilizes a safety-catch vinylsulfonylmethyl resin that is stable under acidic, basic, and heating conditions. Several

solid-phase organic transformations were used to derivatize the indole scaffold. Further work involving library synthesis and biological testing is in progress.

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Supporting Information Available: LCMS and ^1H NMR of selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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